REMARKS

The claims have been amended to delete multiple dependencies, thereby reducing the overall filing cost, and to place them into proper U.S. claim format. Further, the claims submitted with this application to be prosecuted, and which are amended herein, reflect those claims as amended in the International Application and attached as annexes to the International Preliminary Examination Report (IPER). The marked-up and clean substitute specifications submitted herewith include paragraph numbering, the paragraph labelled "Cross-Reference to Related Application," the final paragraph and other informal changes to place the application in proper U.S. format. No new matter has been added. Prosecution on the merits hereof is respectfully requested.

Respectfully submitted,

Date: June 24, 2005

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Christine Kotran

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant	:	Franz Guck & Gieselher Warnke
Serial No.	:	
Filing Date	:	Herewith
Examiner	:	
Group Art Unit:		
Title	:	CONTROLLED DOSAGE AEROSOLS WITH LECITHIN AS SURFACE-ACTIVE AGENT (as amended herein)
Attorney File	:	RO4077US (#90568)

Mail Stop PCT
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia, 22313-1450

MARKED-UP SUBSTITUTE SPECIFICATION

DOSING AEROSOLS CONTAINING LECITHIN AS A SURFACE-ACTIVE SUBSTANCE

BACKGROUND OF THE INVENTION

Cross-Reference to Related Applications

[00001] This application is a National Stage application of International Application No. PCT/EP2003/014901, filed on December 24, 2003, which claims priority of German application number 102 60 882.2, filed on December 24, 2002.

Field of the Invention

[00002] The subject matter of the present invention is controlled dosage aerosols which comprise at least one medicinal agent as well as a mixture made of pressure-liquefied isobutane as propellant and lecithin as surface-active agent.

[00003] The present invention more particularly relates to controlled dosage aerosols comprising at least one medicinal agent with anti-asthmatic action from the group of the glucocorticoids as well as a mixture made of pressure-liquefied isobutane as propellant and lecithin.

Description of the Prior Art

[00004] Aerosol pressurized gas packs, also called controlled dosage aerosols or metered aerosols for short, which are produced and employed by using liquefied pressure gases or compressed gases as a propellant, have been known for a long time. Generally, such metered aerosols consist of a pressure vessel, ~~preferably~~ such as of metal or glass, having a valve construction for withdrawing its content, and of the actual agent to be sprayed, which in most cases consists of an active substance solution as well as [[of]] a propellant in the form of a gas or a gas mixture liquefied under pressure. The pressure-liquefied gas or pressure-liquefied gas mixtures should ideally be miscible with the active substance at any ratio so that one single liquid phase is formed. As an alternative, the pressure-liquefied gas or gas mixture should form a suspension with the active substance which can be shaken easily and above which a gas phase forms. Depending on the agent contained, these metered aerosols are used in the cosmetic and medical fields, or as a room spray, insecticidal spray, and the like.

[00005] The propellants of controlled dosage aerosols have to satisfy special requirements. They must by no means react with the components of the

active agent solution. Also, the propellants must be non-irritating and non-toxic. Fluorochlorinated hydrocarbons had proved particularly suitable. However, because of their ozone-depleting effect it has been necessary to develop alternative propellants.

[00006] However, the quality of these alternative agents must be comparable to that of the fluorochlorinated hydrocarbons; above all, they must be both non-injurious to health and ecologically compatible. Initially, partially halogenated fluorochlorinated hydrocarbons were frequently propagated as replacements but these still have an unacceptably high ozone-depleting ability.

[00007] DE 41 32 176 discloses controlled dosage aerosols for administering isoprenalin derivatives, the so-called ß-sympathomimetics, or the non-steroid anti-inflammatory agent DNCG wherein isobutane is employed as a propellant.

[00008] DE 199 11 064 discloses controlled dosage aerosols containing broncholytic and/or anti-inflammatory agents from the group of the glucocorticoids, with isobutane as propellant and oleic acid or Span 85 as surface-active substances. These dosage aerosols, however, have the disadvantage of a dissatisfactory resuspensibility and of too quick a sedimentation of the active substance in the propellant.

SUMMARY OF THE INVENTION

[00009] ~~It was thus the~~ An object of the present invention to provide a controlled dosage aerosol for medicinal agents, especially for anti-asthmatic medicinal agents from the group of the glucocorticoids which does not have the disadvantages of the controlled dosage aerosols known from DE 199 11 064.

DETAILED DESCRIPTION OF THE INVENTION

[000010] It was surprisingly found that the adjuvant lecithin leads to a marked improvement of the resuspensibility of medicinal agents, especially of glucocorticoids in isobutane.

[000011] Lecithins are glycerophospholipides that are made from fatty acids, glycerol, phosphoric acid and choline. Naturally occurring lecithins are derivatives of 1,2-diacyl-sn-glycerol-3-phosphoric acid. When extracting lecithin from biological material one always obtains a mixture of lecithins that differ from each other by the different fatty acid esters.

[000012] According to the present invention, ~~the preferred~~ an advantageous lecithin is soybean lecithin, which is already widely used in the pharmaceutics industry as an emulsifier.

[000013] In a comparison of the sedimentation behaviour of suspensions of medicinal agent in isobutane under addition of soybean lecithin or various surface-active agents commonly employed in the production of anti-asthmatic metered aerosols it was observed, as will be seen from the below example, that the medicinal agent suspension with soybean lecithin took 10 times longer to sediment than a medicinal agent suspension with oleic acid, and 5 times longer than a medicinal agent suspension with Span 85.

[000014] In further tests, with a ratio of medicinal agent to soybean lecithin of 1:2, 1:1 or 1:0.5, no differences were observed in the sedimentation time, so that a ratio of medicinal agent to soybean lecithin of 1:0.5 may advantageously be chosen.

EXAMPLE

[000015] Comparison of the suspension behaviour of suspensions of medicinal agent in isobutane, using various surface-active agents

	Relative sedimentation
Glucocorticoid : oleic acid (100:1)	1
Glucocorticoid : Span 85 (1:1)	2
Glucocorticoid : soybean lecithin (1:2)	10
Glucocorticoid : soybean lecithin (1:1)	10
Glucocorticoid : soybean lecithin (1:0.5)	10

[000016] In further tests, the following formulations have turned out to be especially advantageous:

Formulation 1:	Glucocorticoid	0.1% -	0.2%
	Lecithin	0.05% -	0.4%
	Isobutane	99.85% -	99.4%
Formulation 2:	Glucocorticoid	0.5% -	1.0%
	Lecithin	0.25% -	4.0%
	Isobutane	99.75% -	95.0%

[000017] For the glucocorticoid beclomethasone diproprionate, the following formulation has been found useful:

Formulation 3:	Beclomethasone	0.1% -2.5%	
	Soybean lecithin	0.05% -	5.0%
	Isobutane	99.85% -	92.5%

[000018] For budesonide the following formulation has been found extremely useful:

Formulation 4:	Budesonide	0.1% -	2.5%
	Soybean lecithin	0.05% -	5.0%
	Isobutane	99.85% -	92.5%

[000019] All quantities relate to percent by weight.

[000020] The inventive aerosols may be prepared by mixing the various components under conditions in which the propellant and the surfactant are liquid and in which the active agent is present in a solid phase.

[000021] The suspension of medicinal agent is filled through the valve into the clinched tin under pressure, which tin at the beginning of the filling process has room temperature. The suspension has a temperature of approx. -10 to +10 °C. Subsequently, the tin is filled up with the propellant, thereby cleaning the valve at the same time.

[000022] The controlled dosage aerosols according to the present invention may be used in the treatment of humans and animals, in particular in the treatment of allergic diseases of the respiratory tract, such as asthma or allergic rhinitis (hay fever), ~~preferably~~ such as by ~~means of~~ oral or nasal inhalation.

[000023] What has been described above are preferred aspects of the present invention. It is of course not possible to describe every conceivable combination of components or methodologies for purposes of describing the present invention, but one of ordinary skill in the art will recognize that many further combinations and permutations of the present invention are possible. Accordingly, the present invention is intended to embrace all such alterations, combinations, modifications, and variations that fall within the spirit and scope of the appended claims.